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New Drugs

Evolution of carfilzomib dose and schedule in patients with multiple myeloma: A historical overview

Andrzej J. Jakubowiak *

Section of Hematology/Oncology, University of Chicago Medical Center, 5841 S Maryland Avenue, MC 2115, Chicago, IL 60637-6613, United States

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ABSTRACT

Carfilzomib is a proteasome inhibitor that binds selectively and irreversibly to its target. In July 2012, carfilzomib received accelerated approval in the United States for the treatment of relapsed and refractory multiple myeloma. Based on emerging preclinical data and clinical results, the total dose, infusion time, and administration schedule of carfilzomib have evolved during phase I and phase II clinical studies, with the aim of optimizing the risk-benefit profile of the agent. Based on in vitro and in vivo findings and encouraging phase I tolerability data, a consecutive-day, twice-weekly dosing schedule was implemented early in the development program. Other phase II studies have led to further refinements in the dosing schedule of carfilzomib, resulting in the current approved schedule for carfilzomib to be administered intravenously over 2–10 min on 2 consecutive days each week for 3 weeks of a 28-day cycle. Prolonged infusion over 30 min has also been assessed in clinical studies to enable the use of higher carfilzomib doses with the aim of improving drug tolerability and efficacy. These data collectively informed the dosing and scheduling schemas for carfilzomib in ongoing trials, including phase I and II studies of combination regimens, and the randomized phase III trials ASPIRE, FOCUS, ENDEAVOR, and CLARION. Additional studies are underway to examine alternative dosing schedules (e.g., once-weekly dosing [CHAMPION-1]).

Introduction

Carfilzomib is a selective proteasome inhibitor that produces sustained inhibition of the chymotrypsin-like activity of the constitutive proteasome and immunoproteasome [1,2], proteasomal variants that are important targets in the treatment of hematologic malignancies [3]. In phase I and phase II clinical studies, carfilzomib demonstrated robust and durable efficacy and an acceptable safety and tolerability profile in patients with relapsed and/or refractory multiple myeloma (MM) [4–10], leading to the accelerated approval of carfilzomib in the United States in 2012 for the treatment of relapsed and refractory MM [11]. This paper reviews the clinical development of carfilzomib (Tables 1 and 2; Fig. 1), with a particular emphasis on the evolution of dose and schedule during phase I and phase II clinical studies in relapsed and/or refractory MM, including the pivotal PX-171-003-A1 (003-A1) clinical study [11].

Preclinical data supporting phase I studies

Preclinical studies provided the basis for phase I clinical testing of carfilzomib in the treatment of hematologic malignancies (Onyx Pharmaceuticals, unpublished results) [1,3,4]. In rodents and monkeys, dosing on 2 consecutive days (QD × 2; e.g., days 1, 2, 8, 9, 15, and 16 of a 28-day cycle) or 5 consecutive days (QD × 5; e.g., days 1–5 of a 14-day cycle) using bolus intravenous (IV) schedules led to cumulative inhibition of proteasome activity (Onyx Pharmaceuticals, unpublished results) [1]. In further support of consecutive daily dosing, mice with established xenograft tumors that received carfilzomib (5–10 mg/kg) on a consecutive day schedule (i.e., days 1 and 2) demonstrated reductions in tumor growth, while a once-weekly or twice-weekly (i.e., days 1 and 4) schedule that allowed for full proteasome recovery between doses was less effective [1]. As doses up to 5 mg/kg (QD × 2) and doses up to 2 mg/kg (QD × 5) were well tolerated in tumor-bearing animals [1], both schedules warranted further investigation in clinical trials. A starting dose level of 1.2 mg/m^2, representing one-tenth of the severely toxic dose in 10% of rats [4], was selected for phase I investigation.

* Tel.: +1 (773) 795 6613; fax: +1 (773) 702 3002.
E-mail address: ajakubowiak@medicine.bsd.uchicago.edu

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Table 1
Completed clinical studies of carfilzomib in MM.

	PX-171-001	PX-171-002	PX-171-003-A0	PX-171-003-A1	PX-171-004 BTZ-treated	PX-171-004 BTZ-naive	PX-171-005
Phase	I	I	II	II	II	II	II
Registration number	–	NCT00150462	NCT00511238	NCT00511238	NCT00530816	NCT00530816	NCT00721734
Age, y	⩾18	⩾18	⩾18	⩾18	⩾18	⩾18	⩾18
Diagnosis	Relapsed or refractory MM[a]	Relapsed or refractory MM[a]	Relapsed and refractory IgG or IgA MM	Relapsed and refractory IgG, IgA, IgE, or IgD MM	Relapsed and/or refractory MM	Relapsed and/or refractory MM	Relapsed and/or refractory MM
Number of prior anti-MM therapies	⩾2	⩾2	⩾2	⩾2	1–3	1–3 (no prior BTZ)	⩾2
ECOG PS	0–2	0–2	0–2	0–2	0–2	0–2	0–2
Hematologic parameters	WBCs ⩾ 2000/mm^3, ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	WBCs ⩾ 2000/mm^3, ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	WBCs ⩾ 2000/mm^3, ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	WBCs ⩾ 2000/mm^3, ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	WBCs ⩾ 2000/mm^3, ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	WBCs ⩾ 2000/mm^3, ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	WBCs ⩾ 2000/mm^3, ANC ⩾ 1000/mm^3, Hb ⩾ 7.0 g/dL, platelets ⩾ 30,000/mm^3
Organ function	Adequate hepatic function; CrCl ⩾ 30 mL/min	Adequate hepatic function; CrCl ⩾ 30 mL/min	Adequate hepatic function; CrCl ⩾ 30 mL/min	Adequate hepatic function; CrCl ⩾ 30 mL/min	Adequate hepatic function; CrCl ⩾ 30 mL/min	Adequate hepatic function; CrCl ⩾ 30 mL/min	Adequate hepatic function; patients were grouped according to renal function, ranging from normal to chronic dialysis
Dosing schedule	QD × 5[b]	QD × 2[c]	QD × 2[c]	QD × 2[c]	QD × 2[c]	QD × 2[c]	QD × 2[c]
Carfilzomib dose, cycle 1 (mg/m^2)	1.2–20.0	1.2–27.0 (dose-escalation phase); 20 on D1, 2 then 27 thereafter (dose-expansion phase)	20	20	20	20	15
Carfilzomib dose, cycle 2 and beyond (mg/m^2)	1.2–20.0	1.2–27.0 (dose-escalation phase); 27 (dose-expansion phase)	20	27	20	20, 27	20, 27[d]
Additional treatment[e]	None	None (dose-escalation phase); none or dexamethasone (20 mg) before each carfilzomib dose for up to 12 cycles (dose-expansion phase)	None	None	None	None	None
Infusion time, min	1–2	1–2	2–10	2–10	2–10	2–10	2–10

ANC, absolute neutrophil count; BTZ, bortezomib; CrCl, creatinine clearance; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; Ig, immunoglobulin; min, minutes; MM, multiple myeloma; QD, consecutive days; WBCs, white blood cells; y, year.
[a] Patients with non-Hodgkin's lymphoma, Hodgkin's lymphoma, or Waldenström's macroglobulinemia were also enrolled.
[b] D1–5 of 14-day cycle.
[c] D1, 2, 8, 9, 15, 16 of 28-day cycle.
[d] 20 mg/m^2 for cycle 2 and 27 mg/m^2 for cycle 3 and beyond, if tolerated.
[e] Patients in 002, 003, 004, 005, and the single-agent cohorts of 007 also received dexamethasone (4 mg) as premedication before each dose of carfilzomib in cycle 1 as prophylaxis against first-dose infusion reactions.

Phase I studies

The initial phase I studies PX-171-001 (001) and PX-171-002 (002; NCT00150462) were undertaken in parallel to assess the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of carfilzomib in patients with relapsed or refractory hematologic malignancies (see Table 1) [4,5].

PX-171-001

The phase I study 001 began in October 2005 (first patient, first visit [FPFV]) and ended in July 2007 (last patient, last visit [LPLV]; see Fig. 1). In 001, single-agent carfilzomib was administered on a QD × 5 schedule as an IV infusion over 1–2 min (see Table 1) [4]. Patients were enrolled in cohorts of 3 to receive carfilzomib in a dose-escalating fashion to a maximum planned dose of 20 mg/m^2 (1.2, 2.4, 4, 6, 8.4, 11, 15, and 20 mg/m^2).

PX-171-002 (NCT00150462)

The phase I study 002 began in September 2005 (FPFV) and ended in January 2009 (LPLV; see Fig. 1). In 002, single-agent carfilzomib was administered on a QD × 2 schedule as an IV infusion over 1–2 min for a maximum of 12 cycles [5]. As in 001, escalating dose levels started at 1.2 mg/m^2 and increased to 2.4, 4, 6, 8.4, 11, 15, and 20 mg/m^2; in addition, 002 had a maximum planned dose of 27 mg/m^2.

Dose escalation in 002 was followed by dose expansion at the maximum planned or maximum tolerated dose (MTD). The dose expansion phase included a single-agent carfilzomib cohort and a carfilzomib plus dexamethasone cohort. Patients received carfilzomib at 20 mg/m^2 on days 1 and 2 of cycle 1, and were to be dose-escalated to a target dose of 27 mg/m^2 thereafter (20/27-mg/m^2 cohort). In the carfilzomib plus dexamethasone cohort, patients received 20 mg oral dexamethasone before each carfilzomib dose.

Table 2
Key ongoing studies of carfilzomib in MM that were informed by the results of phase I/II trials.

	PX-171-006	PX-171-007	CARMYSAP	ASPIRE	FOCUS	ENDEAVOR	CLARION	CHAMPION-1
Phase	Ib/II	Ib/II	I/II	III	III	III	III	I/II
Registration number	NCT00603447	NCT00531284	NCT01279694	NCT01080391	NCT01302392	NCT01568866	NCT01818752	NCT01677858
Age, y	⩾18	⩾18	>65	⩾18	⩾18	⩾18	⩾18	⩾18
Diagnosis	Relapsed or progressive MM	Relapsed and/or refractory MM[a]	Newly diagnosed, transplant-ineligible MM	Relapsed MM	Relapsed and refractory MM	Relapsed MM	Newly diagnosed, transplant-ineligible MM	Relapsed or refractory MM
Number of prior anti-MM therapies	1–3	⩾2	0	1–3	⩾3	1–3	0	1–3
ECOG PS	0–2	0–2	0–2	0–2	0–2	0–2	0–2	0 or 1
Hematologic parameters	ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	ANC ⩾ 1000/mm^3, platelets ⩾ 30,000/mm^3, Hb ⩾ 7.0 g/dL	ANC ⩾ 1000/mm^3, platelets ⩾ 50,000/mm^3	ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	WBCs ⩾ 1500/mm^3, ANC ⩾ 1000/mm^3, Hb ⩾ 7.5 g/dL, platelets ⩾ 30,000/mm^3	ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3	ANC ⩾ 1000/mm^3, Hb ⩾ 8.0 g/dL, platelets ⩾ 50,000/mm^3
Organ function	Adequate hepatic function; CrCl ⩾ 50 mL/min	Adequate hepatic function; CrCl ⩾ 20 mL/min	Adequate hepatic function; CrCl > 30 mL/min	Adequate hepatic function; CrCl ⩾ 50 mL/min	Adequate hepatic function; CrCl ⩾ 15 mL/min	Adequate hepatic function; CrCl ⩾ 15 mL/min	Adequate hepatic function; CrCl ⩾ 15 mL/min	Adequate hepatic function; CrCl ⩾ 30 mL/min
Dosing schedule	QD × 2[b]	QD × 2[b]	QD × 2[c]	QD × 2[b]	QD × 2[b]	QD × 2[b]	QD × 2[c]	QW[d]
Carfilzomib dose, cycle 1 (mg/m^2)	15, 20, or 20 on D1, 2 only, then 27 thereafter (dose-escalation phase); 20 on D1, 2, then 27 thereafter (dose-expansion phase)	20 on D1, 2, then 36–70 thereafter (dose-escalation phase) or 45–56 thereafter (dose-expansion phase)	20 on D1, 2, then 20–45 thereafter (dose-escalation phase) or 36 thereafter (dose-expansion phase)	20 on D1, 2, then 27 thereafter	20 on D1, 2, then 27 thereafter	20 on D1, 2, then 56 thereafter	20 on D1 & 2 of cycle 1, then 36 thereafter	20 on D1 of cycle 1, then 45–88 thereafter (dose-escalation phase); or MTD thereafter (dose-expansion phase)
Carfilzomib dose, cycle 2 and beyond (mg/m^2)	15, 20, or 27 (dose-escalation phase) or 27 (dose-expansion phase) through cycle 12, then biweekly (D1, 2, 15, and 16) for subsequent cycles	36–70 (dose-escalation phase); 45–56 (dose-expansion phase)	20–45 (dose-escalation phase); 36 (dose-expansion phase)	27 through cycle 12, then biweekly (D1, 2, 15, and 16) for cycles 13–18	27; may begin biweekly dosing (D1, 2, 15, and 16) in cycle 10 at investigator discretion	56	36	45–88 (dose-escalation phase); MTD (dose-expansion phase)
Additional treatment	Lenalidomide (10, 15, 20, or 25 mg [dose-escalation phase]; 25 mg [dose-expansion phase] on D1–21) and low-dose dexamethasone (40 mg/week)	None; or weekly low-dose dexamethasone (40 mg) from cycle 1 onwards	Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) on D1–4	Lenalidomide (25 mg on D1–21) and low-dose dexamethasone (40 mg/week) for all cycles	None	Low-dose dexamethasone (40 mg/week)	Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) on D1–4	Low-dose dexamethasone (40 mg on D1, 8, 15, and 22 of cycle 1–8, and on D1, 8, 15 of cycle 9 and beyond)
Infusion time, min	2–10	2–10; or 30	30	2–10	2–10	30	30–60	30

ANC, absolute neutrophil count; CrCl, creatinine clearance; D, day; ECOG, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; min, minutes; MM, multiple myeloma; MTD, maximum tolerated dose; QD, consecutive days; QW, once-weekly dosing; WBCs, white blood cells; y, year.

[a] Patients with solid tumors and refractory or rituximab-intolerant lymphoma were also enrolled.

[b] D1, 2, 8, 9, 15, 16 of 28-day cycle.

[c] D1, 2, 8, 9, 22, 23, 29, 30 of 42-day cycle.

[d] D1, 8, 15 of 28-day cycle.

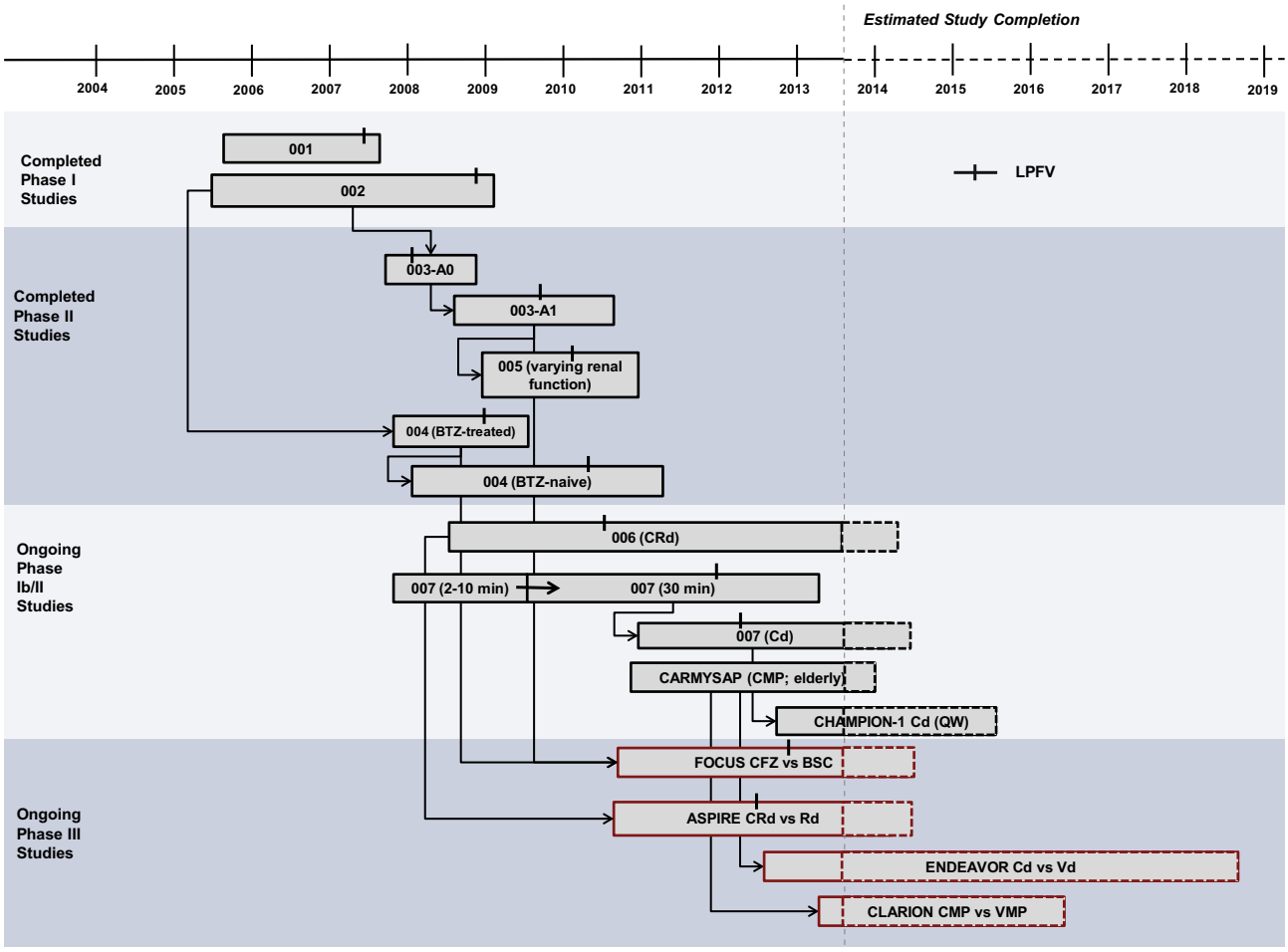

Fig. 1. Clinical timeline for carfilzomib. Safety and efficacy results from phase I and II trials informed the study design of the phase III trials. BSC, best supportive care; BTZ, bortezomib; Cd, carfilzomib and dexamethasone; CMP, carfilzomib, melphalan, and prednisone; CRd, carfilzomib, lenalidomide, and dexamethasone; LPLV, last patient, first visit; min, minutes; QW, once-weekly dosing; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

Patients with MM in the 20/27-mg/m^2 single-agent carfilzomib cohort who did not respond or failed to achieve at least a partial response by cycle 2 or a complete response by cycle 4 were permitted to receive 20 mg oral dexamethasone before each dose of carfilzomib (120 mg/cycle).

Safety and tolerability

Differences in the tolerability profiles of both dosing schedules were apparent. In 001, the most common toxicities were grade 1/2 fatigue and gastrointestinal events, whereas hematologic toxicities were more frequently observed in 002. Notably, grade 3/4 peripheral neuropathy was not reported at high rates in either study, a finding that was also observed in later studies. The 001 study established the MTD of carfilzomib as 15 mg/m^2; in contrast, the MTD was not reached in the 002 study. Based on evidence of anti-MM activity at the 27-mg/m^2 dose and a preliminary analysis of safety data, the dose-expansion phase of the 002 trial was amended to evaluate the escalated dosing approach noted above (dose escalation from 20 to 27 mg/m^2 on day 8 of cycle 1). This approach was found to be well tolerated in 6 patients with no dose-limiting toxicities observed.

In a small number of patients, administration of carfilzomib on either dosing schedule was associated with what was considered at the time to be tumor lysis syndrome (TLS)-like reactions during cycle 1 and first-dose-like effects. TLS-like reactions were characterized by a constellation of symptoms that included increased lactate dehydrogenase, hyperuricemia, hyperphosphatemia, hypocalcemia, hyperkalemia, and renal failure. First-dose-like effects included the following events/symptoms: influenza-like illness, cytokine release syndrome, infusion-related reaction, pyrexia, chills, feeling hot, flushing, dyspnea, hypotension, hypoxia, arthralgia, or myalgia. The initial concerns regarding TLS and first-dose-like effects were mitigated in patients receiving single-agent carfilzomib by the prophylactic use of very-low-dose dexamethasone (4 mg; patients receiving dexamethasone 20 mg before each dose of carfilzomib did not receive the prophylactic dose) and hydration in cycles 1 and 2. Patients also received 250–500 mL IV saline or other appropriate IV fluid prior to each dose, with an additional 250–500 mL as needed after administration of carfilzomib. IV hydration could be continued beyond cycle 2 if deemed necessary [5].

Pharmacokinetics/pharmacodynamics

PK assessments from both phase I studies revealed no significant differences between the 2 dosing schedules in key PK parameters (e.g., maximum concentration [C_{max}], half-life [$t_{1/2}$], area under the curve [AUC], steady-state volume of distribution) [4,5]. PD results were also similar between the 2 studies, with administration on both schedules resulting in 70–80% proteasome

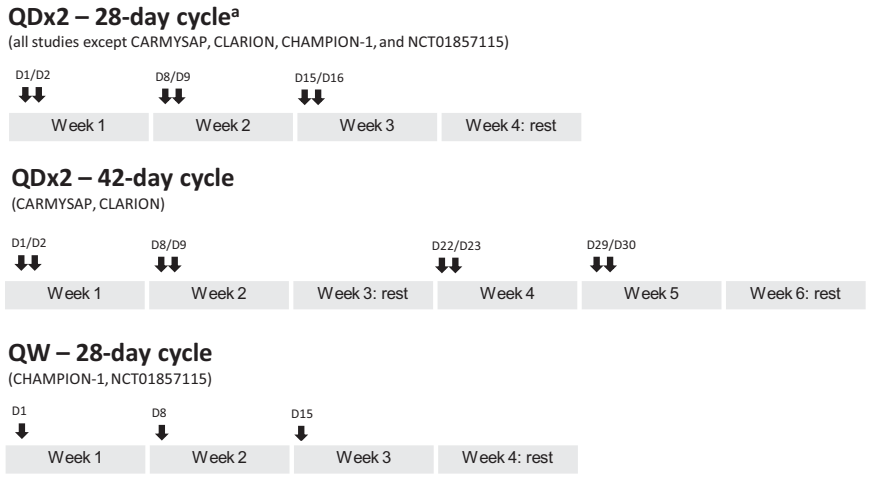

Fig. 2. Carfilzomib schedules examined in completed and ongoing trials. Carfilzomib has been administered using a variety of schedules in completed and ongoing trials. [a]Corresponds to the carfilzomib administration schedule approved by the United States Food and Drug Administration [11]. Recommended cycle 1 dose is 20 mg/m^2; if tolerated, it is recommended to increase dose to 27 mg/m^2 for cycle 2 and subsequent cycles. D, day; QD, consecutive days; QW, once-weekly dosing.

inhibition in whole blood and peripheral blood mononuclear cells at carfilzomib doses of 15 mg/m^2 and higher [4,5].

Efficacy

Although not a primary objective of the initial phase I trials, encouraging objective responses were observed in both studies. In the 001 study, 4 responses (minimal response or better) were noted in patients with MM ($n = 2$), Waldenström's macroglobulinemia ($n = 1$), and mantle cell lymphoma ($n = 1$) [4]. In the 002 study, 8 responses were observed in patients with MM ($n = 7$) and Waldenström's macroglobulinemia ($n = 1$) [5].

Implications of phase I findings on phase II dosing and administration schedule

The results from the 2 phase I studies suggested that consecutive-day dosing had antitumor efficacy, regardless of the schedule used (QD × 2 or QD × 5), corroborating preclinical evidence for substantial proteasome inhibition with either regimen [1]. In addition, the dose-escalation/expansion portions of the phase I trials allowed detailed evaluation of safety at each dosing level. Taking the safety findings and the preliminary efficacy data together, a more favorable risk-benefit profile was observed with the QD × 2 schedule compared with the QD × 5 schedule. Thus, the QD × 2 schedule was chosen for further exploration in phase II studies [6–9].

Concerns about TLS and first-dose-like effects observed in 001 and with the 20/27-mg/m^2 dosing schedule in 002 led to the conservative selection of the 20-mg/m^2 dose of carfilzomib for the first pilot phase II study (PX-171-003-A0 [003-A0]). In addition, prophylactic measures (prehydration and administration of very-low-dose dexamethasone [4 mg] in cycle 1) were implemented to mitigate against these potential adverse events [6].

Phase II studies

PX-171-003-A0 and PX-171-003-A1 (NCT00511238)

While the 002 trial was still ongoing, the phase II 003-A0 pilot study was initiated in August 2007 (FPFV) in patients with relapsed and refractory MM. To be eligible, patients were required to have immunoglobulin (Ig) G (IgG) or IgA MM that was relapsed and refractory after at least 2 prior treatment regimens that must have included the proteasome inhibitor bortezomib and an immunomodulatory agent (see Table 1). Following the initial findings from 002, 20-mg/m^2 carfilzomib was administered IV (QD × 2) for a minimum of 2 cycles (Fig. 2); patients with stable disease or better could continue to receive treatment for a maximum of 12 cycles. Based on emerging preclinical toxicity data demonstrating a reduction in the risk of first-dose-like effects with longer infusion durations (Onyx Pharmaceuticals, unpublished results), the administration time used in 001 and 002 was increased from 1–2 min to 2–10 min in 003-A0 as well as other studies initiated around the same time (e.g., 003-A1, PX-171-004 [004], and PX-171-005 [005]).

In the 46 patients studied in 003-A0, carfilzomib (20 mg/m^2) was well tolerated and first-dose-like effects were not observed [6]. Importantly, the PD parameters were similar to those observed in the 2 phase I studies. The dose and QD × 2 schedule demonstrated encouraging efficacy with an overall response rate (ORR) of 16.7% (95% confidence interval [CI], 7.0–31.4).

During the course of 003-A0, data from the dose-expansion phase of the 002 study became available, demonstrating the safety and tolerability of carfilzomib on the same schedule, but with a dose of 27 mg/m^2 starting on day 8 of cycle 1 for patients who had tolerated the 20-mg/m^2 dose. In addition, preliminary response data from both phase I studies suggested that higher doses might be more efficacious. The 003-A0 pilot study was subsequently amended (003-A1) in July 2008 to permit escalated dosing to 27 mg/m^2 starting with cycle 2 (dose escalation would subsequently be introduced at day 8 of cycle 1 in later studies, when dose escalation was found to be well tolerated). The same QD × 2 dosing schedule and TLS prophylaxis measures were used in 003-A1 as in the original 003-A0 study [7]. The study cohort was expanded and ultimately led to the enrollment of 266 patients. Eligibility criteria for 003-A1 were identical to those for 003-A0, with the exception that patients with IgE or IgD MM were also eligible for enrollment [11]. No differences in tolerability were observed relative to the 003-A0 study and, importantly, there were no incidents of TLS following the implementation of further refined prophylaxis guidelines (including the option to receive prophylactic allopurinol). Patients in the 003-A1 study who received higher doses of carfilzomib (27 mg/m^2) appeared to experience improved response rates relative to 003-A0 (ORRs of 23.7% and 16.7%, respectively) [7]. These findings would ultimately form the foundation of

the accelerated approval for carfilzomib in the United States for this difficult-to-treat patient population.

PX-171-004 (NCT00530816)

The 004 study (FPFV, September 2007; LPLV, January 2011) ran concurrently with the 002, 003-A0, and 003-A1 studies. Patients with MM who had responded to standard first-line therapy and had relapsed and/or refractory disease after at least 1 (but no more than 3) previous regimens were enrolled [8,9]. As with 003-A0 and 003-A1, concerns about the potential for TLS and first-dose-like effects led to an initial selection of the 20-mg/m^2 dose for evaluation, as well as the implementation of prophylactic measures, including prehydration and very-low-dose dexamethasone (4 mg) in cycle 1. Patients were treated with 20 mg/m^2 carfilzomib administered IV over 2–10 min QD × 2 in 28-day cycles for a maximum of 12 cycles. The study initially enrolled patients irrespective of previous exposure to bortezomib. In 35 bortezomib-treated patients, carfilzomib was well tolerated and did not exacerbate preexisting peripheral neuropathy. Importantly, TLS and first-dose-like effects were not observed. The ORR was 17.1% and the clinical benefit response rate was 31.4%, demonstrating the efficacy of this dose and schedule [8].

Based on encouraging safety and efficacy results from 002 at 27 mg/m^2, the decision was made to increase the dose of carfilzomib in the 004 study (similar to the study amendment made to 003-A0). Thus, patients who tolerated 20 mg/m^2 carfilzomib during cycle 1 received 27 mg/m^2 over 2–10 min beginning in cycle 2. To distinguish 004 from the 003-A1 study, which also administered 20/27 mg/m^2 carfilzomib to patients with relapsed or refractory MM, a study amendment in December 2008 restricted enrollment to those patients who had not been previously exposed to bortezomib (i.e., "bortezomib-naive" patients), ultimately enrolling 129 patients [9]. No differences in tolerability were observed relative to the bortezomib-treated patients in 004 [8,9]. Two cases of TLS were observed during cycle 1 in patients treated at 20 mg/m^2; after these events occurred, prophylactic hydration was implemented on the basis of emerging safety results from the 002 study, demonstrating success in limiting this adverse event. Although the study was not designed or powered to make comparisons between the dose cohorts with respect to efficacy or safety, it is nonetheless notable that incremental improvements in efficacy were observed between cohorts, with an ORR of 42.4% (95% CI, 29.6–55.9) for 20 mg/m^2 and 52.2% (95% CI, 39.7–64.6) for 20/27 mg/m^2 [9]. Similar improvements were also seen in progression-free survival (8.2 months for 20 mg/m^2 and not reached for 20/27 mg/m^2). To place these data into context, response rates of roughly 40% have been reported with bortezomib monotherapy in 2 phase III studies in patients with relapsed or refractory MM [12,13].

Overall, the results of 004 suggest that carfilzomib is generally tolerable and active in patients with relapsed and/or refractory MM, with higher activity observed in patients who are less heavily pretreated. Similar to what was observed in 003-A1, there was an apparent increase in efficacy in 004 at the 27-mg/m^2 target dose compared with 20 mg/m^2. A pooled analysis of data from the 003-A0, 003-A1, and 004 trials would later show a significant dose–response relationship with single-agent carfilzomib treatment, resulting in a 1.28-fold (95% CI: 1.17–1.40; $p < 0.001$) increase in the odds of achieving a partial response or better for each 1 mg/m^2 increase in carfilzomib dose (equivalent to a 5.52-fold increase in the odds of achieving a response if the average dose increased from 20 mg/m^2 to 27 mg/m^2) [14]. Similar results were also observed after adjusting for various baseline prognostic covariates across studies (e.g., International Staging System stage, female sex, and higher hemoglobin level) for the primary end point of ORR ($p < 0.001$), as well as the secondary end points of duration of response ($p < 0.001$), progression-free survival ($p < 0.001$), and overall survival ($p < 0.001$).

PX-171-005 (NCT00721734)

The phase II trial 005 (see Table 1) ran from December 2008 (FPFV) until December 2010 (LPLV) in parallel with the 002, 003-A0, 003-A1, and 004 studies. The entry criteria were identical to those established for the 003-A1 study, with the exception that patients with varying degrees of renal function were enrolled, ranging from normal renal function to patients requiring chronic hemodialysis [10]. As in 003-A1 and 004, patients received carfilzomib by IV infusion over 2–10 min QD × 2 for a maximum of 12 cycles. As the PK and safety profile of carfilzomib had not been previously evaluated in patients with renal insufficiency or renal dysfunction, a starting dose of 15 mg/m^2 in cycle 1 was selected. If the dose was tolerated, it was increased to 20 mg/m^2 in cycle 2 and to 27 mg/m^2 in cycle 3 and beyond. First-dose and TLS prophylaxis measures were identical to those of the amended 003-A1 and 004 bortezomib-naive studies.

No differences in tolerability were noted among patients with varying degrees of renal impairment. Notably, TLS and first-dose-like reactions were not observed. Efficacy results were encouraging with an ORR of 25.5% and, when patients were grouped by renal function, responses were evident across all groups.

Phase Ib/II study of carfilzomib combined with lenalidomide and low-dose dexamethasone

PX-171-006 (NCT00603447)

Based on preclinical and clinical data supporting the combination of proteasome inhibitors with immunomodulatory drugs and low-dose dexamethasone [15–18], the phase Ib/II study PX-171-006 (006) was initiated in June 2008 to evaluate carfilzomib in combination with lenalidomide and dexamethasone (CRd) in patients with relapsed or progressive MM (Table 2). Patients were treated with CRd in 28-day cycles. Carfilzomib was given as a 2–10-min IV infusion QD × 2. Lenalidomide was given orally (10–25 mg/day) on days 1–21, and oral dexamethasone (40 mg) was given once weekly. The study enrolled patients in dose-escalation cohorts (carfilzomib dose range: 15–27 mg/m^2) and a dose-expansion cohort (20/27 mg/m^2). A total of 84 patients were enrolled, including those previously treated with bortezomib (77% of patients; 18% refractory) and/or lenalidomide (70% of patients; 35% refractory). As the MTD was not reached during the dose-escalation phase, all patients in the dose-expansion cohort ($n = 52$) received the maximum planned dose of 20 mg/m^2 carfilzomib on days 1 and 2 and 27 mg/m^2 thereafter (i.e., from cycle 1 day 8). The trial is anticipated to be completed in 2014 (as of November 2013, 2 patients remain on CRd treatment) [19]. After a median follow-up of 32.7 months, the ORR was 69.0% overall and 76.9% in patients who received the maximum planned dose of carfilzomib (20/27 mg/m^2). Median progression-free survival was 11.8 months overall and 15.4 months in patients receiving the maximum planned dose. Taken together, these findings suggest a potential relationship between dose and response, supporting similar emerging data from 003-A0, 003-A1, and 004 [14]. Notably, response rates and progression-free survival, especially at MTD, compare favorably with those reported for patients treated with lenalidomide and dexamethasone [20–22]. Grade 3/4 adverse events following CRd use were similar to those from earlier studies using single-agent carfilzomib at the 20/27-mg/m^2 dose (including a low rate [1%] of grade 3/4 peripheral neuropathy), demonstrating

that CRd is well tolerated in patients with relapsed or progressive MM.

Phase Ib/II study of prolonged infusion and higher doses

PX-171-007 (NCT00531284)

The PX-171-007 (007) study was initially activated in September 2007 to evaluate the safety and efficacy of carfilzomib in patients with advanced solid tumors, and included dose escalation up to 36 mg/m^2 administered IV over 2–10 min QD × 2 [23]. This higher maximum intended dose was justified by emerging clinical evidence of a possible dose–response relationship, along with the absence of an MTD in other carfilzomib trials and the successful mitigation of TLS and first-dose-like effects with prophylactic interventions. After initiation of 007, preclinical studies demonstrated that a 30-min infusion of 8 mg/kg carfilzomib in rats resulted in a 28-fold lower C_{max} relative to an IV bolus injection, while other PK parameters and proteasome inhibition remained comparable [24]. In addition, while 44% mortality was observed with IV bolus administration in animals, the 30-min infusion was well tolerated and did not result in any deaths. Based on these results, it was hypothesized that prolonging the infusion time may improve safety and possibly enhance efficacy by allowing patients to receive higher doses than those previously evaluated (i.e., >27 mg/m^2). To test this hypothesis, 007 was amended in May 2009 to enroll patients with relapsed or refractory MM, and to administer carfilzomib as a prolonged 30-min infusion with dose escalation beyond 36 mg/m^2. Carfilzomib was administered on a QD × 2 schedule, in which doses on days 1 and 2 of cycle 1 were 20 mg/m^2 followed by cohort escalation to 36, 45, 56, or 70 mg/m^2. Prior to carfilzomib infusion, very-low-dose dexamethasone (4 mg for carfilzomib doses ⩽ 45 mg/m^2 or 8 mg for carfilzomib doses > 45 mg/m^2) was given as premedication to reduce the risk of potential infusion-related reactions (Papadopoulos et al. unpublished results). The results from the dose-escalation phase of 007 established 20/56 mg/m^2 as the MTD, whereupon this cohort was further expanded to a total of 24 patients. The ORR for the expanded 20/56-mg/m^2 cohort was 60%. Supporting the preclinical findings of dose proportionality, PK analysis showed a proportional increase in C_{max} and AUC with increasing dose, but no effect on $t_{1/2}$ or carfilzomib clearance (Papadopoulos K et al. unpublished results).

In 2011, 007 was amended again to examine the tolerability and efficacy of carfilzomib doses higher than 27 mg/m^2 (administered via a 30-min infusion) in patients with MM when combined with low-dose dexamethasone (40 mg/week). In the amended study, the 20/45-mg/m^2 and 20/56-mg/m^2 cohorts were expanded; patients received carfilzomib QD × 2 (as in the previous amendment) and low-dose dexamethasone (40 mg/week). Among patients treated with this combination (N = 22), the ORR was 60.0% and the safety profile was found to be consistent with single-agent carfilzomib at comparable doses (Papadopoulos et al. unpublished results).

Phase I/II trial of carfilzomib combined with melphalan-prednisone

CARMYSAP (NCT01279694)

In many countries outside the United States, particularly in Europe, melphalan and prednisone in combination with a third agent (e.g., bortezomib or thalidomide) is considered a standard treatment regimen for transplant-ineligible patients with newly diagnosed MM. There are a limited number of approved combination regimens available, however, for elderly patients who are newly diagnosed but are not candidates for stem cell transplantation. Thus, the phase I/II CARMYSAP study (NCT01279694) was initiated in France to assess the safety and efficacy of carfilzomib when combined with melphalan and prednisone (CMP) in patients with newly diagnosed MM who were aged >65 years (see Fig. 1 and Table 1) [25]. Combining melphalan and prednisone with bortezomib (VMP) was effective in the VISTA trial, yet a higher rate of adverse events was observed compared with patients who received melphalan and prednisone alone, including an increased rate of peripheral neuropathy (44% vs. 5%; all grades, respectively) [26]. Given the emerging data that single-agent carfilzomib induced a low rate of new-onset peripheral neuropathy and appeared not to exacerbate existing peripheral neuropathy [7,27], it was hypothesized that CMP may be better tolerated than VMP in elderly patients with newly diagnosed MM.

The CARMYSAP study was initiated in October 2010 and is ongoing at the time of writing. In the phase I portion of the study, 20 mg/m^2 carfilzomib was given on days 1 and 2 of cycle 1, followed by dose escalation to a maximum planned dose of 45 mg/m^2 infused over 30 min. While other QD x 2 schedules utilize a 28-day cycle in which carfilzomib is administered for 3 weeks followed by 1 rest week, CARMYSAP uses a 42-day cycle in which carfilzomib is administered for 2 weeks followed by 1 rest week, a pattern that is repeated twice per cycle (i.e., dosing on days 1, 2, 8, 9, 22, 23, 29, and 30) for 9 cycles (see Fig. 2). The use of a 42-day cycle in CARMYSAP was designed to mimic the dosing schedule of VMP used in the VISTA trial. Oral melphalan (9 mg/m^2) and prednisone (60 mg/m^2) are also given on days 1–4. As of January 2013, 69 patients have been enrolled. The MTD for carfilzomib on this schedule has been established at 20/36 mg/m^2 [28]. An ORR of 89% was reported with CMP, which compares favorably with results reported for other melphalan and prednisone-based regimens (ORR range: 71% to 81%) [26,29,30]. Importantly, CMP appears to be well tolerated in elderly patients with newly diagnosed MM, with no reports of grade ⩾2 peripheral neuropathy [25].

Application of findings from phase I and II trials towards ongoing studies

Despite advances in the treatment of MM over the past decade, the disease remains incurable; most patients eventually relapse and exhaust all available treatment options [31]. The need for new therapies is clear, but so is the need for understanding the optimal use of available therapies to maximize patient benefit. This includes evaluating dosing and administration schedules and combination partners to achieve an appropriate balance between efficacy and safety/tolerability.

As is common in drug development, the optimal dosing schedule and administration of carfilzomib have evolved as the drug has progressed through clinical trials and with continued preclinical investigation. In the case of carfilzomib, a QD × 2 dosing schedule was investigated in phase II trials based on 1) preclinical evidence demonstrating greater antitumor activity with sustained proteasome inhibition, and 2) favorable safety and tolerability versus a QD × 5 dosing schedule in preclinical studies and phase I clinical studies. Efficacy and safety results from 003-A1 and safety data from 003-A0, 004, and 005 led to the establishment of a dosing and administration schedule that supported the US accelerated approval of carfilzomib in patients with relapsed and refractory MM in July 2012 (see Fig. 2). In the completed phase II studies, higher doses were administered by modifying the dosing schedule; a lower dose (e.g., 20 mg/m^2) was administered during the first week of treatment, followed by administration of the target dose

Table 3
Application of key phase I and II results to dose and schedule in ongoing studies.

Study	Phase	Treatment	Carfilzomib dose/schedule	Patient population
PX-171–003-A1	II	Carfilzomib	20/27 mg/m^2 (QD x 2[a])	Relapsed and refractory MM
FOCUS (NCT01302392)	III	Carfilzomib vs best supportive care	20/27 mg/m^2 (QD x 2[a])	Relapsed and refractory MM
PX-171–006	Ib/II	CRd	20/27 mg/m^2 (QD x 2[a])	Relapsed or progressive MM
ASPIRE (NCT01080391)	III	CRd vs Rd	20/27 mg/m^2 (QD x 2[a])	Relapsed MM
NCT01029054	I/II	CRd	Up to 36 mg/m^2 (QD x 2[a] cycles 1–8; D1, 2, 15, 16 cycles 9+)	Newly diagnosed MM
NCT01816971	II	CRd	Up to 36 mg/m^2 (QD x 2[a] induction and consolidation; D1, 2, 15, 16 maintenance)	Newly diagnosed MM
NCT01402284	II	CRd	20/36 mg/m^2 (QD x 2[a])	Newly diagnosed MM
NCT01572480	II	CRd	20/36 mg/m^2 (QD x 2[a])	Smoldering MM
CARMYSAP	I/II	CMP	MTD: 20/36 mg/m^2 (QD x 2[b])	Newly diagnosed, transplant-ineligible MM
CLARION (NCT01818752)	III	CMP vs VMP	20/36 mg/m^2 (QD x 2[b])	Newly diagnosed, transplant-ineligible MM
NCT01346787	II	CCyd	20/36 mg/m^2 (QD x 2[a])	Newly diagnosed MM
NCT01857115	I/II	CCyd	Up to 20/70 mg/m^2 (QW[c])	Newly diagnosed MM
PX-171–007	Ib/II	Cd	MTD: 20/56 mg/m^2 (QD x 2[a])	Relapsed and/or refractory MM[d]
ENDEAVOR (NCT01568866)	III	Cd vs Vd	20/56 mg/m^2 (QD x 2[a])	Relapsed MM
NCT01903811	II	Cd	27 mg/m^2 vs 56 mg/m^2 (QD x 2[a])	Relapsed or refractory MM
CHAMPION-1 (NCT01677858)	I/II	Cd	Up to 88 mg/m^2 (QW[c])	Relapsed or refractory MM

CCyd, carfilzomib, cyclophosphamide, and dexamethasone; Cd, carfilzomib and dexamethasone; CMP, carfilzomib, melphalan, and prednisone; CRd, carfilzomib, lenalidomide, and dexamethasone; D, day; MM, multiple myeloma; MTD, maximum tolerated dose; QD, consecutive days; QW, once-weekly dosing; Rd, lenalidomide and dexamethasone; Vd, bortezomib and dexamethasone; VMP, bortezomib, melphalan, and prednisone.

[a] D1, 2, 8, 9, 15, 16 of 28-day cycle.

[b] D1, 2, 8, 9, 22, 23, 29, 30 of 42-day cycle.

[c] D1, 8, 15 of 28-day cycle.

[d] Patients with solid tumors and refractory or rituximab-intolerant lymphoma were also enrolled.

(e.g., 27 mg/m^2) in subsequent weeks. Escalation on day 8 of cycle 1, as evaluated in 006 and 007, demonstrated that earlier dose escalation was also well tolerated. Given the apparent dose–response effect that has been observed, it is possible that additional patients in the early phase 1 and 2 studies may have demonstrated responses if the carfilzomib dose had been escalated at an earlier time point. Although a small number of TLS and first-dose-like effect cases were observed during the phase I and the initial phase II studies, the use of prophylactic hydration, allopurinol, and the addition of low-dose dexamethasone has since reduced the incidence of these effects in later studies, as has extending the infusion time.

Administration of carfilzomib over 30 min and adding a low dose of dexamethasone enabled patients to receive higher doses of carfilzomib in 007, with comparable tolerability to that seen with lower doses and shorter infusion times (Papadopoulos et al. unpublished results) [32,33]. These findings are consistent with a dose–response relationship previously observed in phase I studies and the phase II studies 003-A0, 003-A1, and 004 [4,5,14]. Interestingly, increased immunoproteasome inhibition has been observed with the higher dose of carfilzomib (20/56 mg/m^2), and may be a possible mechanism for the reported improvements in clinical responses, as the immunoproteasome is known to be highly expressed in myeloma cells [15,32].

Results from the studies described above have been used to inform the carfilzomib regimens used in ongoing randomized, controlled, phase III studies and investigator-sponsored trials (Table 3). For example, knowledge from the 003-A1 study was applied to the dosing schedule in the phase III randomized FOCUS trial (NCT01302392), which is investigating single-agent carfilzomib versus best supportive care in relapsed and refractory MM. This trial has been underway since September 2010 (FPFV), with primary completion anticipated for the first half of 2014 [34].

The CRd regimen that was used in 006 is being assessed in the phase III randomized trial ASPIRE (NCT01080391) in comparison with lenalidomide and dexamethasone in relapsed MM [35]. ASPIRE began enrolling patients in June 2010 and primary completion is anticipated for the first half of 2014. CRd is also being investigated in earlier lines of treatment in a number of investigator-sponsored trials. In a phase I/II trial, CRd treatment in patients with newly diagnosed MM (NCT01029054) was shown to have excellent efficacy and depth of response and appeared to be well tolerated [33,36]. Patients received up to 36 mg/m^2 carfilzomib QD × 2 (in cycle 9 and beyond, carfilzomib administration on days 8 and 9 was omitted) over a 30-min infusion, and patients had the option to receive stem cell transplantation after cycle 4. A separate phase II trial is further exploring use of the CRd regimen before and after stem cell transplantation in patients with newly diagnosed MM (NCT01816971). Similar to the initial phase I/II trial, patients receive a target dose of 36 mg/m^2 carfilzomib administered QD × 2 (during maintenance therapy, carfilzomib administration on days 8 and 9 is omitted). CRd is also being investigated in patients with newly diagnosed MM when followed by extended lenalidomide dosing (NCT01402284) [37], and in patients with smoldering MM (NCT01572480) [38]; in both studies, carfilzomib is being administered at 36 mg/m^2 QD × 2 over 30 min.

Tolerability and efficacy findings from the CARMYSAP study [25] have supported additional investigations into combining carfilzomib with an alkylating agent and corticosteroid. The phase III randomized trial CLARION (NCT01818752) is comparing CMP versus VMP in patients with newly diagnosed MM who are ineligible for stem cell transplantation, using the same doses and schedule as the CARMYSAP study. In addition, carfilzomib combined with cyclophosphamide and dexamethasone (CCyd) is being investigated in phase I and II trials, as cyclophosphamide is considered to lack the cumulative hematologic toxicity of melphalan and may be a better-tolerated alternative [39,40]. CCyd is also being evaluated in patients with newly diagnosed MM, with carfilzomib administered QD × 2 at a dose of 20/36 mg/m^2 (NCT01346787) [41] or weekly in doses up to 20/70 mg/m^2 (NCT01857115).

The safety results from the amended 007 study provided the basis for the doses and schedules that are being used in a number

of studies. The phase III randomized trial ENDEAVOR (NCT01568866) is comparing a 30-min infusion of 20/56 mg/m^2 carfilzomib plus dexamethasone versus bortezomib plus dexamethasone in patients with relapsed MM. The study was initiated in June 2012, with primary completion expected for January 2015. Additional studies are investigating the use of dexamethasone in combination with different doses and schedules of carfilzomib, and use of the combination regimen in earlier lines of treatment. For example, a phase II study is examining the efficacy of dexamethasone in combination with 2 different doses of carfilzomib (27 mg/m^2 vs 56 mg/m^2 QD $\times$ 2) in patients with relapsed or refractory MM (NCT01903811). Meanwhile, the ongoing phase I/II study CHAMPION-1 (NCT01677858) is examining dexamethasone combined with higher carfilzomib doses (20/45, 20/56, 20/70, and 20/88 mg/m^2, as a 30-min infusion) that are administered once-weekly in patients with relapsed or refractory MM. At the 2013 American Society of Hematology Annual Meeting and Exposition, the study investigators reported that the MTD of once-weekly carfilzomib administered in combination with dexamethasone (40 mg) was 70 mg/m^2 [42]. An ORR of 60% was observed in patients receiving the MTD ($n = 15$). At the MTD, the regimen was found to have an acceptable safety and tolerability profile, with infrequent grade $\geqslant 3$ adverse events, a low rate of discontinuation due to adverse events, and no carfilzomib dose reductions.

Conclusion

In summary, results from early preclinical and clinical studies have informed ongoing phase II and III randomized trials that are investigating carfilzomib in a number of different dosing regimens, schedules, and treatment combinations. As with any therapeutic, the optimization of dosing regimens and schedules is an important step in realizing the optimal risk-benefit profile of carfilzomib. Further trials of carfilzomib combinations in various MM settings are underway, as are studies of its efficacy and safety in subsets of patients such as those with high-risk cytogenetics [43]. These findings will undoubtedly inform healthcare professionals, patients, and their caregivers about the activity of single-agent carfilzomib and its use in combination with other agents in different patient populations. In addition, findings from ongoing studies may help to minimize the need for dose reductions and treatment discontinuations, which may ultimately lead to deeper and more durable responses.

Conflict of interest statement

AJ has served as on advisory boards or as a consultant for Bristol-Myers Squibb, Celgene, Janssen-Cilag, Onyx Pharmaceuticals, and Millennium Pharmaceuticals. He has also received research funding from Bristol-Myers Squibb, Celgene, Janssen-Cilag, Onyx Pharmaceuticals, Millennium Pharmaceuticals, and Novartis, and received honoraria from Bristol-Myers Squibb, Celgene, Janssen-Cilag, Onyx Pharmaceuticals, and Millennium Pharmaceuticals.

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